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Diastereoselective Synthesis of (Aryloxy)phosphoramidate Prodrugs

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The first diastereoselective synthesis of aryloxyphosphoramidate prodrugs of 3′-deoxy-2′,3′-didehydrothymidine monophosphate (d4TMP) was recently reported. The synthetic approach utilized the chiral auxiliary (*S*)-4-isopropylthiazolidine-2-thione (**2**). For this strategy, a stereochemically pure phosphorodiamidate intermediate was needed. The diastereoselective formation of this key compound was investigated by using different phenols and L-alanine methyl or benzyl ester. Generally, the reaction with 3- or 4-substituted phenols led to significantly better diastereoselectivities compared to their 2-substituted counterparts. Moreover, variation of the ester group in the amino acid residue resulted in no significant differences with regard to the obtained diastereoselectivity. From the reported results, a model for the transition state was elaborated. Finally, eight new (S_P)-arylphosphoramidates were synthesized with very high diastereoselectivities (up to ≥ 95 % *de*) and tested for their anti-HIV potency, showing a tendency for higher antiviral activity from the (S_P) diastereomers.

Introduction

Lipophilic nucleotide precursors (pronucleotides) are a promising alternative to improve the biological activity of nucleoside analogues in antiviral chemotherapy.[1] Pronucleotides allow the intracellular delivery of 5′-nucleotides that need subsequent conversion to the 5′-di- and 5′-triphosphates. The latter are ultimately the biologically active compounds. Several pronucleotide strategies have been reported, for example, the phosphoramidates,[2,3] the *cyclo*Sal-phosphate triesters,[4] the mixed-*S*-acyl-2-thioethyl compounds,[5] the HepDirect technique,[6] and recently the bis(acyloxybenzyl) approach for the intracellular delivery of nucleoside diphosphates.[7] These pronucleotide approaches use different means of activation, for example, by enzymes or chemical cleavage. In the first four cases, the compounds are phosphoric acid derivatives that contain four different residues attached to the phosphorus center. As a consequence of the stereogenic center at the phosphorus atom, diastereomers of the pronucleotides result because of the additional chiral centers in the nucleoside analogs. In these syntheses, pronucleotides are formed as mixtures of two diastereomers, and in most cases, their separation has been a difficult or impossible task. Importantly, in cases where the diastereomers were separable, different biological activity, toxicity, and pharmacokinetic profiles were found for the individual diastereomers.

Sofia et al. recently reported the discovery of phosphoramidate prodrugs of 2′-deoxy-2′-α-fluoro-2′-β-*C*-methyluridine-5′-monophosphate that show strong inhibition of hepatitis C virus (HCV) replication.[8] The prodrugs were prepared as a 1:1 mixture of diastereomers that were separated by chromatography and crystallization. The antiviral evaluation of the individual diastereomers showed that the (S_P) diastereomer was > 10-fold more active against HCV than the (R_P) diastereomer. Significant differences in activity were also found for the phosphoramidates of 2′-*C*-methylcytidine. Again, the compounds were synthesized as mixtures, and then the individual diastereomers were separated by reversed-phase HPLC. The antiviral evaluation of the diastereomers proved that the more lipophilic diastereomer was about 8-fold more active against HCV than the second diastereomer.[9] These examples clearly demonstrate the importance of the phosphorus configuration on the biological activity.

Consequently, the development of strategies for isomerically pure nucleotide prodrugs is important. Recently, we published the first diastereoselective synthesis of *cyclo*Sal-[10] and (aryloxy)phosphoramidate prodrugs **1**.[11] In both cases, the routes led to diastereomerically almost pure prodrugs (≥ 95% *de*), and both pathways were based on the use of chiral auxiliaries. Interestingly, one chiral auxiliary was not suitable for the *cyclo*Sal-pronucleotides; instead, the auxiliary had to be adapted to the target molecule. For the diastereoselective synthesis of phosphoramidates **1**, (*S*)-4-isopropylthiazolidine-2-thione (**2**) was used as the chiral auxiliary.[12] Scheme 1 summarizes the reaction sequence for the synthesis of the nucleoside phosphoramidates **1** starting

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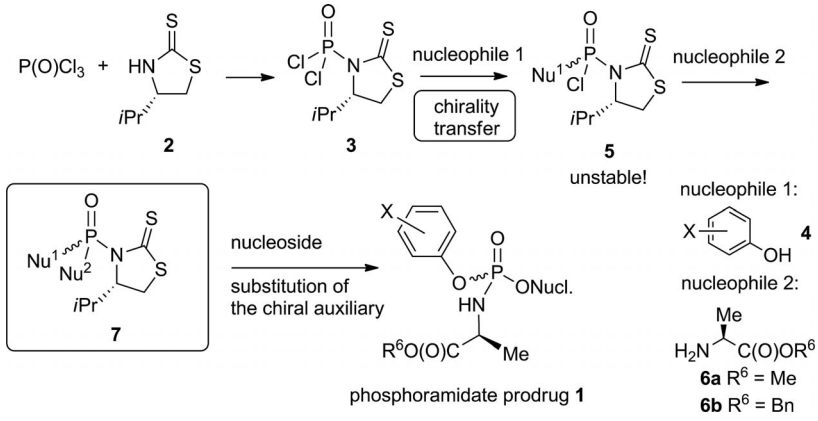

Scheme 1. Diastereoselective route to phosphoramidate prodrugs **1**.

from auxiliary **2** and through achiral phosphorodichloridate **3**, chiral phosphorochloridate **5**, and phosphorodiamidate **7**.[11] The latter compound is the key intermediate of the synthesis, because it is chiral and can be isolated.

The anti-HIV evaluation of the phosphoramidate prodrugs of nucleoside analog 3′-deoxy-2′,3′-didehydrothymidine (d4T) confirmed the expected significant differences in the activities of the individually prepared diastereomers (up to 65-fold).[11] In the recent report, only four different phenols **4** and L-alanine methyl ester (**6a**) were used in the reactions, and significantly different diastereoselectivities were obtained depending on the chosen phenol. Here, a series of phenol derivatives (i.e., **4**) were used to gain more insight into this reaction. Moreover, in addition to methyl ester **6a**, the benzyl ester of L-alanine (**6b**) was also used to expand the synthesis to other phenolic and amino acid residues. Finally, the method was applied to the syntheses of eight new phosphoramidate prodrugs starting from diastereomerically pure phosphorodiamidate intermediates.

Results and Discussion

(*S*)-4-Isopropylthiazolidine-2-thione (**2**), prepared according to the procedure of Delaunay et al.,[13] was treated with an excess of phosphoryl chloride and NEt_3 in CH_2Cl_2 to give phosphorodichloridate **3** (Scheme 1). The crude material **3** displayed only one ^{31}P NMR signal (δ = 3.70 ppm) and thus was used directly in the next reaction. Previously, we reported that the conversion of **3** to the chiral phosphorochloridates **5** was performed using the three phenol derivatives **4b**,**d**,**g** as well as 1-naphthol (**4l**). As mentioned above, the ratio of the two diastereomers obtained in this step, where the chirality transfer took place, was clearly dependent on the phenol derivatives and the reaction conditions.[11]

The proposed transition state shown in Figure 1 should lead to the preferential formation of the (S_P) diastereomer because of the interaction of the bulky isopropyl group with the incoming phenolate nucleophile. A trigonal-bipyramidal intermediate should form from the subsequent displacement of the pro-(R_P)-chloride anion. This proposed transition state is supported by the X-ray crystal structure of thiophosphorodichloridate **8**, which was previously obtained.[14] Here, a series of 2- and 4-donor- or acceptor-substituted phenols along with 3-substituted derivatives (i.e., **4a**–**m**) were studied (Figure 2). The results for the reaction between phosphorodichloridate **3** and **4a**–**m** to yield phosphorochloridates **5** are given in Table 1.

First, the synthesis of the phosphorochloridates **5** was carried out by cooling phosphorodichloridate **3** at –91 °C in the presence of 0.7–1.0 equiv. of the phenols **4** and the base DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) for 25–75 min. The conversion of **3** ranged between a moderate 59% to an excellent 93% depending on the phenol used (Table 1). The phosphorochloridates (R_P/S_P)-**5** were obtained in a ratio of up to 14:1. In all cases, the (S_P)-configured diastereomer was assumed to be preferentially formed

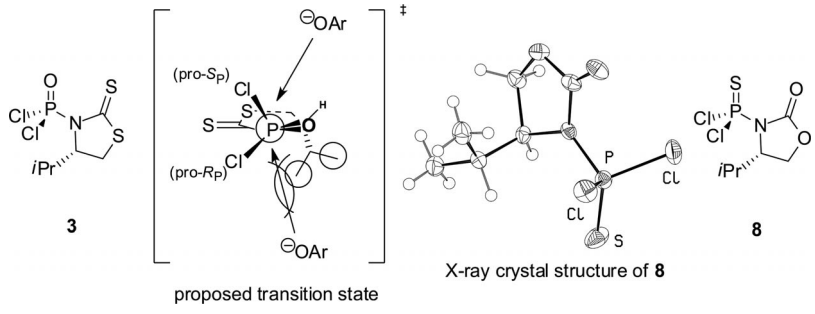

Figure 1. Possible transition state for the preferential formation of (S_P)-**5**.

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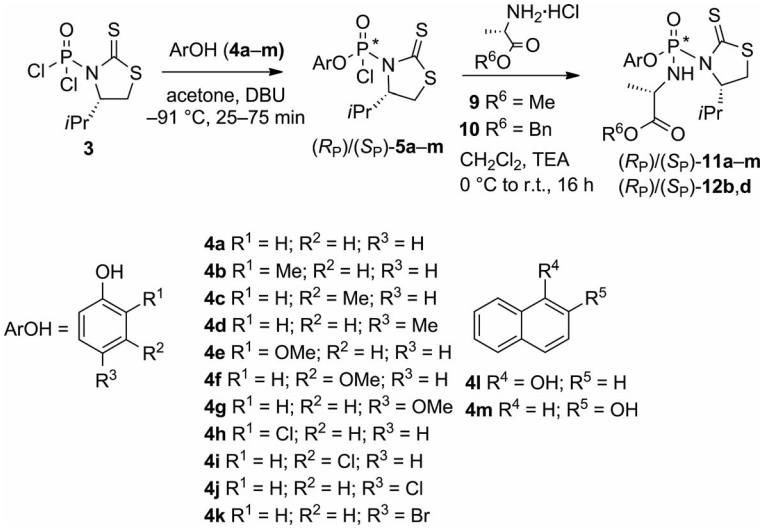

Figure 2. Synthesis of phosphorodiamidate derivatives (R_P)- or (S_P)-**11** and (R_P)- or (S_P)-**12** through phosphorochloridates (R_P)/(S_P)-**5**.

Table 1. Conversion in the reactions leading to **5**, **11**, and **12**, respectively, and the diastereomeric excess values for **5**, **11**, and **12**.

5	Conversion of **3** [%][a]	*de* [%][a]	**11**, **12**[b]	Conversion of **5** [%][a]	*de* [%][a,c]
a	59	83	**11a**	39	74
b	64	51	**11b**	54	30
c	84	83	**11c**	66	81
d	93	81	**11d**	78	81
e	85	87	**11e**	64	85
f	74	86	**11f**	68	78
g	83	72	**11g**	60	72
h	81	28	**11h**	55	15
i	75	67	**11i**	46	25
j	66	75	**11j**	58	52
k	62	66	**11k**	36	44
l	79	36	**11l**	62	28
m	74	77	**11m**	59	72
			12b	95	48
			12d	93	81

[a] Conversion and *de* determined by ^{31}P NMR spectroscopy of the crude mixture. [b] **11** (R^6 = Me), **12** (R^6 = Bn). [c] Starting materials are the phosphorochloridate derivatives **5**.

as a result of the addition/elimination mechanism. Always the resonance signal of the (S_P) diastereomer was found to be low-field-shifted compared to that of the (R_P) isomer [e.g.: (S_P)-**5e**, δ = –2.02 ppm; (R_P)-**5e**, δ = –2.53 ppm; see Exp. Sect.]. Due to their instability, phosphorochloridates **5** were purified only by one fast chromatography on a short silica gel column and could not be separated into the individual diastereomers. The diastereomeric ratio was found to be strongly dependent on the substitution of the aromatic moiety. Particularly, 2-methylphenol (**4b**) and 2-chlorophenol (**4h**) led to a significant reduction in diastereoselectivity (51% *de* and 28% *de*, respectively). To our surprise, 2-methoxyphenol (**4e**) gave the best value (87% *de*) for all the reactions. This unexpected difference may be attributed to the different electronic and/or steric properties of the chloro, methyl, and methoxy groups. Moreover, these experiments also showed pronounced differences between the diastereomeric ratios in the cases of 1- and 2-naphthol [**4l** and **4m** yielding **5l** (36% *de*) and **5m** (77% *de*), respectively]. Overall, the 2-substituted systems led to markedly lower diastereoselectivities. The use of substoichiometric amounts was particularly necessary in the cases of phenols **4c**,**f**,**h**–**k**. If 1.0 equiv. of these phenols was used, considerable amounts of diarylphosphoramidates **13** were observed as side products. For the other phenols **4**, compounds **13** were formed in only very small amounts or not at all. The avoidance of the formation of diarylphosphoramidates **13** was of great importance, because compounds **13** and the phosphorochloridates **5** showed identical R_f values and consequently could not be separated by column chromatography. As a result, the diastereoselective synthesis of **5** worked best by using the 3- and 4-substituted phenol derivatives. With the exception of 2-methoxy, 2-substituted phenols led to poor diastereoselectivities and thus are not suitable for this diastereoselective synthesis. This loss of diastereoselectivity could be related to the proposed transition state, although a final explanation cannot be given (Figure 1).

Next, the syntheses of phosphorodiamidates (R_P)- and (S_P)-**11** and (R_P)- and (S_P)-**12** (**11**, R^6 = Me; **12**, R^6 = Bn) were carried out by using the diastereomerically enriched

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mixtures of phosphorochloridates **5a**–**m** and L-alanine methyl or benzyl ester hydrochloride (**9** and **10**, respectively). L-Alanine was previously identified as the most effective amino acid for use in this phosphoramidate approach, and the different esters in the amino acid moiety also play an important role for the antiviral potency. The reaction began by the addition of NEt_3 at 0 °C, and then the reaction mixture was stirred at room temperature for 16 h (Figure 2). The conversion of phosphorochloridates **5** and the diastereomeric excesses obtained for phosphorodiamidates **11** and **12** are also given in Table 1. In all cases, the major diastereomer has the (R_P) configuration, which was supported earlier by three X-ray crystal structure analyses.[11] In comparison to **5**, the (R_P) isomers of **11** or **12** displayed the low-field ^{31}P NMR signal compared to their (S_P) counterparts [e.g.: (S_P)-**11d**, δ = 1.43 ppm; (R_P)-**11d**, δ = –0.83 ppm; see Exp. Sect.].[11] Interestingly in all cases, except for **11d** and **12d**, the diastereomeric excess values were found to be lower as compared to those of the starting mixture of diastereomers **5** (Table 1) which points to some isomerization during the second substitution of the amino acid ester. In contrast to compounds **5**, the phosphorodiamidates **11** and **12** were sufficiently stable to be purified and separated to give the stereochemically pure diastereomers by silica gel column chromatography (≥ 95% *de* for each diastereomer).

Again, the substitution pattern in the aromatic residue played a role with regard to the observed diastereoselectivities. Particularly, the 2-methylphenol phosphorodiamidate derivative of the L-alanine methyl ester **11b** was obtained in a drastically lower diastereoselectivity compared to phosphorochloridate **5b**. A reason for the loss in stereospecificity may be related to the presence of diarylphosphoramidate **13**. In all reactions of phosphorochloridates **5** leading to the phosphorodiamidates **11**, some amounts of **13** were additionally formed. This was clearly proven by ^{31}P and ^{1}H NMR spectroscopy and mass spectrometry. However, no traces of the phenols were detected in the ^{1}H NMR spectroscopic data of **5**. It was reported previously that phosphoramidates **13** can also undergo substitution reactions (Figure 3, pathway b).[15] In contrast to compounds **5**, diaryl derivative **13** is an achiral compound with two identical phenol groups. Thus, a reaction of **13** with the amino acid ester should lead to a diastereomeric mixture of the target compounds **11**, which consequently lowers the overall diastereospecificity of this reaction. In addition, it is still unknown to what extent the leaving group differentiation between the chloride and the phenolate moieties in starting material **5** can be achieved. Assuming that a small fraction of the reaction of **5** with the amino acid esters **9** and **10** took place with displacement of the phenolate, one should expect intermediate **14** as a product (Figure 3, pathway c). This material should be formed with inversion of configuration at the P atom. In a subsequent step, the released phenolate can then react with compound **14** with displacement of the chloride anion and again with inversion of configuration. In total, this scenario would lead to the products **11** with the inverted configuration (Figure 3, pathway a). However, the released phenolate could react with the starting material **5** to lead to the diaryl derivative **13**, again. Therefore, both proposed reactions would lead to a reduction in the stereochemical purity of the obtained phosphorodiamidates **11**.

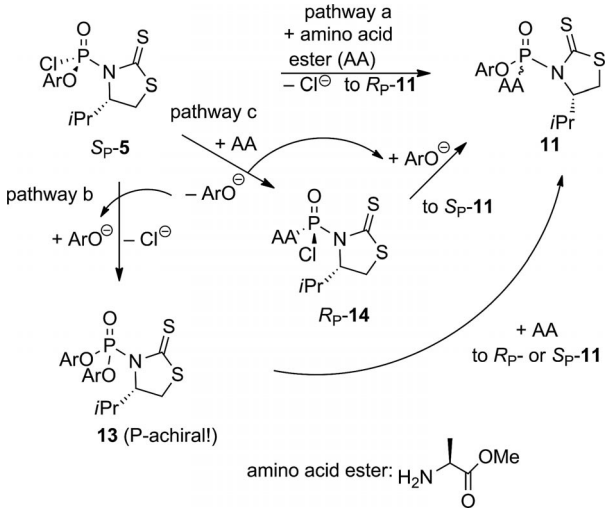

Figure 3. Proposed formation of side products **13** and **14** in the synthesis of phosphorodiamidates **11**.

To prove whether diarylphosphoramidates like **13** react with the amino acid ester, a separate experiment was carried out (Figure 4). However, by using an identical experimental setup, no formation of the expected phosphorodiamidates (R_P)-**11d** or (S_P)-**11d** was detected. The ^{31}P NMR spectrum of the crude reaction mixture showed no conversion at all. Thus, this experiment excludes that the loss of stereoselectivity is related to the formation of compound **13**. Intermediate **14** still may play a role in the decrease of stereoselectivity (Figure 3); however, the synthesis and isolation of inter-

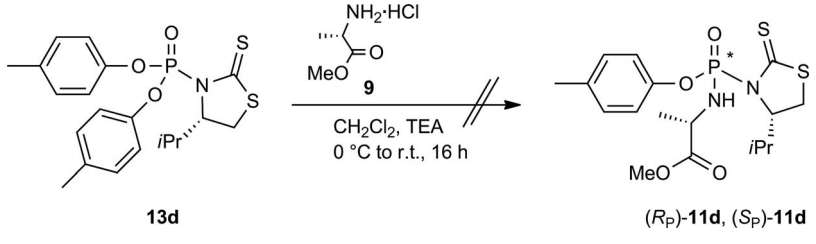

Figure 4. Excluded reaction to the formation of phosphorodiamidates **11d**.

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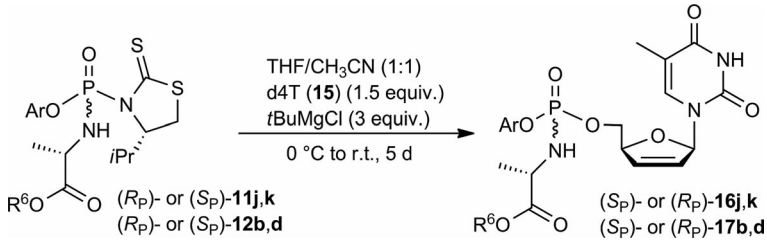

Figure 5. Synthesis of d4T-phosphoramidates **16j**,**k** and **17b**,**d**.

mediate **14** was unsuccessful. Thus, it is impossible to give a final proof of the reaction mechanism explaining the formation of the minor diastereomer (S_P)-**11**.

Nevertheless, the formation of intermediate **14** can be proven indirectly by the preparation of diaryl derivative **13**. If **14** is formed, 1 equiv. of phenol would be released, which then could react in a subsequent reaction to give achiral compounds **13** as well as the diastereomer of **11**. Interestingly, the use of L-alanine benzyl ester hydrochloride **10**, which was prepared according to the procedure of Joullié et al.,[16] did not lead to the formation of diaryl derivative **13**. Its use led to very high conversions and almost to the same diastereomeric excess values as those of **5b**,**d** (**12b**, 48% *de*; **12d**, 81% *de*).

For the following reaction, phosphorodiamidates **11j**,**k** and **12b**,**d** were separately treated with 3′-deoxy-2′,3′-didehydrothymidine (d4T, **15**) to give phosphoramidate prodrugs **16j**,**k** and **17b**,**d** (Figure 5). The reactions were carried out in a mixture of THF/CH_3CN (1:1) with the addition of *tert*-butylmagnesium chloride. The Grignard reagent was used as a base analogous to Uchiyama's method.[17]

Table 2 shows the isolated yields and diastereomeric purities of phosphoramidate prodrugs **16j**,**k** and **17b**,**d**. The (S_P) configuration at the phosphorus atom is supported by comparison with the X-ray crystal structure of phosphoramidate prodrug (S_P)-PSI-7977.[8] Furthermore, this X-ray analysis supports our previously proposed reaction mechanism for this base-induced substitution as being an addition/elimination reaction occurring at the phosphorus atom and proceeding with inversion of configuration, for example, (R_P)-**11** to (S_P)-**16** and (R_P)-**12** to (S_P)-**17**.[12] The diastereomeric excess values were determined by ^{31}P NMR after column chromatography and were found to be at least 85% *de*. Except for the 85% *de* value for phosphoramidate prodrug (R_P)-**17b**, the diastereomeric values almost corresponded to the ≥ 95% *de* in the starting materials.

Table 2. Yields and diastereomeric excess values of phosphoramidate prodrugs **16j**,**k** and **17b**,**d**.

(S_P)	δ(^{31}P) [ppm]	Yield[a] [%]	*de*[b] [%]	(R_P)	δ(^{31}P) [ppm]	Yield[a] [%]	*de*[b] [%]
16j	3.13	20	95	**16j**	2.62	26	≥ 95
16k	3.13	15	93	**16k**	2.56	50	≥ 95
17b	2.98	11	≥ 95	**17b**	2.59	28	85
17d	3.27	14	94	**17d**	2.62	44	≥ 95

[a] Isolated yields. [b] *de* determined by ^{31}P NMR spectroscopy after purification.

Antiviral Evaluation

Phosphoramidates **16j**,**k** and **17b**,**d** were evaluated for their anti-HIV activity in vitro. All compounds showed activity against HIV-1 and HIV-2 in wild-type CEM/0 cell cultures at a concentration range that was often superior to that of the parental d4T (Table 3).

Moreover, it was interesting to observe that both diastereomeric prodrugs of d4T kept full antiviral activity against HIV-2 in TK-deficient CEM/TK$^-$ cells. In general, the 4-substituted (S_P) diastereomers **16j**,**k**, and **17d** were found to be more active than the (R_P) diastereomers (5-fold in the case of **16j**,**k** and 3-fold for **17d** against HIV-2 in CEM/TK-deficient cells). However, in the case of 2-methyl-substituted phosphoramidate prodrugs **17b**, the diastereomers showed almost identical antiviral values.

Table 3. Antiviral activity of phosphoramidates **16j**, **k** and **17b**, **d**.

	EC_{50} [μM][a]			CC_{50} [μM][b]
	CEM/0[c]		CEM/TK$^-$[d]	CEM/0
	HIV-1(III_B)	HIV-2(ROD)	HIV-2(ROD)	
(S_P)-**16j**	0.021 ± 0.0085	0.030 ± 0.014	0.035 ± 0.0078	54 ± 2.8
(R_P)-**16j**	0.13 ± 0.071	0.18 ± 0.028	0.18 ± 0.099	190 ± 18
(S_P)-**16k**	0.042 ± 0.030	0.074 ± 0.0035	0.031 ± 0.013	60 ± 4.2
(R_P)-**16k**	0.14 ± 0.078	0.17 ± 0.064	0.14 ± 0.085	144 ± 2.1
(S_P)-**17b**	0.45 ± 0.12	0.58 ± 0.0071	0.45 ± 0.0	101 ± 8.5
(R_P)-**17b**	0.19 ± 0.035	0.40 ± 0.0	0.27 ± 0.0	98 ± 11
(S_P)-**17d**	0.029 ± 0.024	0.073 ± 0.0078	0.047 ± 0.028	71 ± 4.9
(R_P)-**17d**	0.11 ± 0.035	0.11 ± 0.035	0.13 ± 0.071	115 ± 9.2
d4T (**15**)	0.51 ± 0.31	0.89 ± 0.11	140 ± 16	> 250

[a] Antiviral activity in T-lymphocytes, 50% effective concentration. [b] Cytostatic activity, 50% cytostatic concentration. [c] Wild-type CEM/0 cells. [d] Thymidine kinase deficient CEM TK$^-$ cells.

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Conclusions

The diastereospecific synthesis of phosphoramidate prodrugs **16j**,**k** and **17b**,**d** was achieved by starting from stereochemically pure phosphorodiamidates **11** and **12**. These key compounds were synthesized diastereoselectively in three steps by using the chiral auxiliary (*S*)-4-isopropylthiazolidine-2-thione (**2**). The formation of this key compound was studied by investigating its dependence on different phenol derivatives **4a**–**m** and the L-alanine methyl or benzyl ester hydrochloride (**9** and **10**, respectively) attached to the phosphorodiamidate moiety. The variation of the phenolic residues led to the proposed transition state shown in Figure 1, explaining the preferential formation of (S_P)-configured phosphorochloridate derivatives **5**. In addition, it was observed that 3- and 4-substituted phenol derivatives led to significantly better diastereoselectivities compared to 2-substituted phenols, which gave mostly poor stereoselectivities. The variation of the amino acid ester residues did not lead to significant differences with regard to the diastereoselectivity. Finally, eight new (S_P)-arylphosphoramidates were synthesized as diastereomerically pure compounds and tested for their antiviral activity. Interestingly, the (S_P)-4-substituted phosphoramidates were found to be antivirally markedly more active than their (R_P) counterparts, independent of the substituent, demonstrating again the importance of diastereoselective access to these compounds. In contrast, the 2-methyl derivatives were equipotent for unknown reasons. Work to study the properties of the individual diastereomers is currently ongoing in our laboratories.

Experimental Section

General: All experiments were conducted under scrupulously dry conditions and under nitrogen. The solvents CH_2Cl_2, CH_3CN, and NEt_3 were distilled from CaH_2 and stored over molecular sieves. Et_2O and THF (tetrahydrofuran) were distilled from sodium or potassium benzophenone and stored over molecular sieves. Acetone was distilled from phosphorus pentoxide and stored over molecular sieves. DBU was distilled under nitrogen and stored over molecular sieves. The petroleum ether (boiling range 50–70 °C), EtOAc, CH_2Cl_2, and CH_3OH employed in chromatography were distilled before use. For column chromatography, silica gel 60 (230–400 mesh) was used. Thin layer chromatography was performed on precoated aluminium plates 60 F_{254} with a 0.2 mm layer of silica gel containing a fluorescence indicator. The NMR spectroscopic data were recorded with 400 or 500 MHz spectrometers (AMX 400 or DRX 500). All ^1H and ^{13}C NMR chemical shifts are quoted in ppm and were calibrated by solvent signals. ^{31}P NMR chemical shifts are quoted in ppm by using H_3PO_4 as an external reference. High-resolution mass spectra were obtained with a VG Analytical VG/70-250F spectrometer (FAB, *m*-nitrobenzyl alcohol matrix). HR-ESI spectra were obtained with an Agilent Technologies ESI-TOF 6224 spectrometer. Analytical HPLC was carried out with a VWR-Hitachi LaChromElite HPLC system consisting of a VWR-Hitachi 2130 Pump, autosampler, and VWR-Hitachi UV detector 2455. The column used was a Nucleodur C18 Isis, 5 μm (Macherey–Nagel). Elution was performed by using a water/acetonitrile (Sigma–Aldrich, HPLC grade) eluent: 0–80% CH_3CN (0–60 min), 80–0% CH_3CN (60–65 min), 0% CH_3CN (65–70 min), a flow rate of 0.5 mL/min, and UV detection at 265 nm. The purity of phosphoramidate prodrugs **16** and **17** was checked by using HPLC, and in all cases was ≥ 95%.

Preparation of [(4*S*)-4-Isopropyl-2-thioxo-1,3-thiazolidin-3-yl]phosphonic Dichloride (3): A solution of (4*S*)-4-isopropyl-1,3-thiazolidine-2-thione (**2**, 0.80 g, 4.96 mmol) and phosphoryl chloride (1.39 mL, 14.8 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C. NEt_3 (0.76 mL, 5.45 mmol) in CH_2Cl_2 (12 mL) was added dropwise. Following the addition, the reaction mixture was warmed to room temperature and stirred for 16 h. The solvent was removed under reduced pressure by using a high-vacuum pump, and the residue was suspended in CH_2Cl_2 (1 mL) and Et_2O (15 mL). The precipitated triethylammonium chloride was filtered under nitrogen and washed with Et_2O (5 mL). The solvent of the filtrate was removed under reduced pressure by using a high-vacuum pump to give the crude product **3** as an oil. Further purification was not possible due to high reactivity, and the ^{31}P NMR spectrum showed only one signal at δ = 3.70 ppm.

General Procedure A. Preparation of Aryl [(4*S*)-4-Isopropyl-2-thioxo-1,3-thiazolidin-3-yl]phosphonochloridates 5: A solution of **3** (1.0 equiv.) and the phenol or 1-naphthol derivative **4** (0.7 or 1.0 equiv.) in acetone was cooled to –91 °C. DBU (1.0 equiv.) was added dropwise to the vigorously stirred solution. After 25–75 min (dependent on **4**) at –91 °C, the reaction was quenched – without allowing it to warm to room temperature – with saturated ammonium chloride solution (approximately 10 mL) and extracted with CH_2Cl_2 (3×). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure by using a high-vacuum pump. The resulting residue was purified immediately by very quick column chromatography (1.5 cm diameter, 54.5 cm length) on silica gel (approximately 23 g) using petroleum ether (boiling range 50–70 °C)/EtOAc (2:1). The solvent was removed under reduced pressure by using a high-vacuum pump. Further purification of **5** was not possible due to the decomposition of the chiral auxiliary **2**.

General Procedure B. Preparation of Alanine Derivatives 11 and 12: A suspension of **5** (1.0 equiv.) and L-alanine methyl ester hydrochloride (**9**, 1.0 equiv.) or L-alanine benzyl ester hydrochloride (**10**, 1.0 equiv.) in CH_2Cl_2 was cooled to 0 °C. NEt_3 (3.0 equiv.) was added dropwise. Following the addition, the reaction mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with a saturated ammonium chloride solution and the mixture extracted with CH_2Cl_2 (3×). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure by using a rotary evaporator. The resulting residue was purified by column chromatography on silica gel [petroleum ether (boiling range 50–70 °C)/EtOAc, 2:1].

General Procedure C. Preparation of Thymidine Derivatives 16 and 17: A solution of d4T (**15**, 1.5 equiv.) in THF/CH_3CN (1:1) was cooled to 0 °C. *tert*-Butylmagnesium chloride (1.7 M solution in THF, 3.0 equiv.) was added dropwise. Following the addition, the reaction mixture was warmed to room temperature and stirred for 30 min. A solution of **11** or **12** (1 equiv.) in THF/CH_3CN (1:1) was added to the nucleoside suspension at 0 °C. Following the addition, the reaction mixture was warmed to room temperature and stirred for 5 d. The reaction was quenched with saturated ammonium chloride solution and the mixture extracted with CH_2Cl_2 (3×). The combined organic layers were dried with magnesium sulfate and concentrated under reduced pressure by using a rotary evaporator. The resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH, 39:1). The product was freeze-dried.

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5a: According to General Procedure A, compound **3** (1.38 g, 4.96 mmol) and phenol (**4a**, 0.47 g, 4.96 mmol) were dissolved in acetone (9.2 mL). After the addition of DBU (0.75 mL, 4.96 mmol), the reaction mixture was stirred at –91 °C for 40 min. Product **5a** was obtained as a yellow oil (1.57 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.35 (m, 2 H, Ar), 7.34–7.27 (m, 3 H, Ar), 5.03–4.93 (m, 1 H, 4-H), 3.66 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 3.18–3.11 (m, 1 H, 5′-H), 2.58–2.43 (m, 1 H, 6-H), 1.13 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H), 1.09 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.73, –1.61 (*dr* = 1:9.6; 81% *de*) ppm.

5c: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 3-methylphenol (**4c**, 0.27 mL, 2.60 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.39 mL, 2.60 mmol), the reaction mixture was stirred at –91 °C for 75 min. Product **5c** was obtained as a yellow oil (1.08 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.20 (m, 2 H, Ar), 7.11–7.02 (m, 2 H, Ar), 4.99–4.93 (m, 1 H, 4-H), 3.62 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 3.15–3.10 (m, 1 H, 5′-H), 2.54–2.43 (m, 1 H, 6-H), 2.33 (s, 3 H, Ph-Me), 1.09 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 1.06 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.71, –1.84 (*dr* = 12:1; 85% *de*) ppm.

5e: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 2-methoxyphenol (**4e**, 0.41 mL, 3.72 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.56 mL, 3.72 mmol), the reaction mixture was stirred at –91 °C for 45 min. Product **5e** was obtained as a yellow oil (1.21 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 1 H, Ar), 7.24–7.17 (m, 1 H, Ar), 7.02–6.90 (m, 2 H, Ar), 5.07–5.01 (m, 1 H, 4-H), 3.89 (s, 3 H, Ph-OMe), 3.72 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 5-H), 3.21–3.14 (m, 1 H, 5′-H), 2.60–2.47 (m, 1 H, 6-H), 1.13 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 1.08 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –2.02, –2.53 (*dr* = 19.8:1; 90% *de*) ppm.

5f: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 3-methoxyphenol (**4f**, 0.29 mL, 2.60 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.39 mL, 2.60 mmol), the reaction mixture was stirred at –91 °C for 75 min. Product **5f** was obtained as a yellow oil (0.96 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 1 H, Ar), 6.94-6.80 (m, 3 H, Ar), 5.01–4.95 (m, 1 H, 4-H), 3.80 (s, 3 H, Ph-OMe), 3.66 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 3.19–3.11 (m, 1 H, 5′-H), 2.56–2.46 (m, 1 H, 6-H), 1.12 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 1.09 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.66, –1.92 (*dr* = 14.1:1; 87% *de*) ppm.

5h: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 2-chlorophenol (**4h**, 0.33 g, 2.60 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.39 mL, 2.60 mmol), the reaction mixture was stirred at –91 °C for 52 min. Product **5h** was obtained as a yellow oil (1.11 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.44 (m, 2 H, Ar), 7.33–7.26 (m, 1 H, Ar), 7.24–7.18 (m, 1 H, Ar), 5.11–5.02 (m, 1 H, 4-H), 3.83–3.69 (m, 1 H, 5-H), 3.27–3.17 (m, 1 H, 5′-H), 2.59–2.43 (m, 1 H, 6-H), 1.14 (d, $^3J_{H,H}$ = 6.6 Hz, 3 H, 7-H or 8-H), 1.09 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.94, –2.83 (*dr* = 2:1; 34% *de*) ppm.

5i: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 3-chlorophenol (**4i**, 0.33 g, 2.60 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.39 mL, 2.60 mmol), the reaction mixture was stirred at –91 °C for 60 min. Product **5i** was obtained as a yellow oil (0.80 g, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 4 H, Ar), 5.01–4.94 (m, 1 H, 4-H), 3.67 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 3.21–3.14 (m, 1 H, 5′-H), 2.53–2.45 (m, 1 H, 6-H), 1.10 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 1.07 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.85 ppm.

5j: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 4-chlorophenol (**4j**, 0.33 g, 2.60 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.39 mL, 2.60 mmol), the reaction mixture was stirred at –91 °C for 52 min. Product **5j** was obtained as a yellow oil (0.93 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H, Ar), 7.21–7.16 (m, 2 H, Ar), 4.93–4.85 (m, 1 H, 4-H), 3.57 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 4.2 Hz, 1 H, 5-H), 3.14–3.04 (m, 1 H, 5′-H), 2.49–2.34 (m, 1 H, 6-H), 1.04 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 1.00 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.53, –1.58 (*dr* = 5.9:1; 70% *de*) ppm.

5k: According to General Procedure A, compound **3** (1.73 g, 6.20 mmol) and 4-bromophenol (**4k**, 0.75 g, 4.34 mmol) were dissolved in acetone (11.5 mL). After the addition of DBU (0.65 mL, 4.34 mmol), the reaction mixture was stirred at –91 °C for 50 min. Product **5k** was obtained as a yellow oil (0.93 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.42 (m, 2 H, Ar), 7.23–7.13 (m, 2 H, Ar), 5.00–4.92 (m, 1 H, 4-H), 3.70–3.61 (m, 1 H, 5-H), 3.33–3.23 (m, 1 H, 5′-H), 2.53–2.39 (m, 1 H, 6-H), 0.99 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.96 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.75, –1.81 (*dr* = 4.5:1; 64% *de*) ppm.

5m: According to General Procedure A, compound **3** (1.03 g, 3.72 mmol) and 2-naphthol (**4m**, 0.54 g, 3.72 mmol) were dissolved in acetone (6.9 mL). After the addition of DBU (0.56 mL, 3.72 mmol), the reaction mixture was stirred at –91 °C for 45 min. Product **5m** was obtained as a colorless solid (0.93 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.77 (m, 4 H, Ar), 7.56–7.44 (m, 3 H, Ar), 5.05–5.00 (m, 1 H, 4-H), 3.65 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H), 3.15 (dd, $^2J_{H,H}$ = 11.5 Hz, $^4J_{H,H}$ = 2.5 Hz, 1 H, 5′-H), 2.60–2.50 (m, 1 H, 6-H), 1.14 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 1.11 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.46, –1.65 (*dr* = 26.8:1; 93% *de*) ppm.

(R_P)-11a and (S_P)-11a: General Procedure B was applied by using compound **5a** (0.55 g, 1.65 mmol), L-alanine methyl ester hydrochloride (**9**, 0.23 g, 1.65 mmol), and NEt_3 (0.69 mL, 4.95 mmol) in CH_2Cl_2 (2.4 mL). (R_P)-**11a**: Product (R_P)-**11a** was obtained as a colorless oil (0.17 g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 4 H, Ar), 7.22–7.16 (m, 1 H, Ar), 5.10 (dd, $^2J_{H,P}$ = 8.9 Hz, $^3J_{H,H}$ = 8.9 Hz, 1 H, NH-Ala), 4.99–4.92 (m, 1 H, 4-H), 4.26–4.13 (m, 1 H, CH-Ala), 3.69–3.62 (m, 1 H, 5-H), 3.65 (s, 3 H, MeO-Ala), 3.17–3.09 (m, 1 H, 5′-H), 2.39–2.27 (m, 1 H, 6-H), 1.43 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 0.98 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, 7-H or 8-H), 0.88 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.91 ppm. (S_P)-**11a**: Product (S_P)-**11a** was obtained as a colorless oil (0.03 g, 5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 4 H, Ar), 7.24–7.17 (m, 1 H, Ar), 5.39 (dd, $^2J_{H,P}$ = 8.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, NH-Ala), 4.64–4.56 (m, 1 H, 4-H), 4.34–4.21 (m, 1 H, CH-Ala), 3.73 (s, 3 H, MeO-Ala), 3.16 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 2.98–2.92 (m, 1 H, 5′-H), 2.40–2.27 (m, 1 H, 6-H), 1.38 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 1.00 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.97 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.36 ppm.

(R_P)-11c and (S_P)-11c: General Procedure B was applied by using compound **5c** (0.98 g, 2.80 mmol), L-alanine methyl ester hydro-

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chloride (**9**, 0.39 g, 2.80 mmol), and NEt_3 (1.17 mL, 8.40 mmol) in CH_2Cl_2 (4.0 mL). (R_P)-**11c**: Product (R_P)-**11c** was obtained as a colorless oil (0.45 g, 38%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.17 (m, 1 H, Ar), 7.13–7.08 (m, 2 H, Ar), 7.01–6.97 (m, 1 H, Ar), 5.10 (dd, $^2J_{H,P}$ = 8.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, NH-Ala), 4.98–4.92 (m, 1 H, 4-H), 4.24–4.14 (m, 1 H, CH-Ala), 3.68–3.61 (m, 1 H, 5-H), 3.65 (s, 3 H, MeO-Ala), 3.16–3.10 (m, 1 H, 5′-H), 2.39–2.29 (m, 1 H, 6-H), 2.34 (s, 3 H, Ph-Me), 1.42 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala), 0.98 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 0.90 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –1.00 ppm. (S_P)-**11c**: Product (S_P)-**11c** was obtained as a colorless oil (0.05 g, 5%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.18 (m, 1 H, Ar), 7.13–7.07 (m, 2 H, Ar), 7.02–6.99 (m, 1 H, Ar), 5.37 (dd, $^2J_{H,P}$ = 8.8 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH-Ala), 4.65–4.56 (m, 1 H, 4-H), 4.33–4.21 (m, 1 H, CH-Ala), 3.72 (s, 3 H, MeO-Ala), 3.18 (dd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 3.01–2.92 (m, 1 H, 5′-H), 2.39–2.28 (m, 1 H, 6-H), 2.34 (s, 3 H, Ph-Me), 1.38 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 1.00 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.97 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.26 ppm.

(R_P)-11e and (S_P)-11e: General Procedure B was applied by using compound **5e** (0.85 g, 2.31 mmol), L-alanine methyl ester hydrochloride (**9**, 0.32 g, 2.31 mmol), and NEt_3 (0.96 mL, 6.95 mmol) in CH_2Cl_2 (3.3 mL). (R_P)-**11e**: Product (R_P)-**11e** was obtained as a colorless oil (0.28 g, 28%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 1 H, Ar), 7.17–7.11 (m, 1 H, Ar), 6.96–6.86 (m, 2 H, Ar), 5.33 (dd, $^2J_{H,P}$ = 8.8 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH-Ala), 5.06–4.99 (m, 1 H, 4-H), 4.22–4.08 (m, 1 H, CH-Ala), 3.87 (s, 3 H, Ph-OMe), 3.69–3.61 (m, 1 H, 5-H), 3.63 (s, 3 H, MeO-Ala), 3.20–3.14 (m, 1 H, 5′-H), 2.64–2.53 (m, 1 H, 6-H), 1.41 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala), 1.09 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 1.06 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.11 ppm. (S_P)-**11e**: Product (S_P)-**11e** was obtained as a colorless oil (0.015 g, 2%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 1 H, Ar), 7.18–7.09 (m, 1 H, Ar), 6.98–6.84 (m, 2 H, Ar), 5.32 (dd, $^2J_{H,P}$ = 8.8 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH-Ala), 4.79–4.73 (m, 1 H, 4-H), 4.33–4.20 (m, 1 H, CH-Ala), 3.87 (s, 3 H, MeO-Ala), 3.72 (s, 3 H, Ph-OMe), 3.45 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 3.06–3.03 (m, 1 H, 5′-H), 2.46–2.36 (m, 1 H, 6-H), 1.34 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala), 1.03 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 0.99 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.01 ppm.

(R_P)-11f and (S_P)-11f: General Procedure B was applied by using compound **5f** (0.80 g, 2.20 mmol), L-alanine methyl ester hydrochloride (**9**, 0.31 g, 2.20 mmol), and NEt_3 (0.92 mL, 6.60 mmol) in CH_2Cl_2 (3.1 mL). (R_P)-**11f**: Product (R_P)-**11f** was obtained as a colorless oil (0.36 g, 38%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.14 (m, 1 H, Ar), 6.91–6.83 (m, 2 H, Ar), 6.75–6.67 (m, 1 H, Ar), 5.09 (dd, $^2J_{H,P}$ = 7.5 Hz, $^3J_{H,H}$ = 7.5 Hz, 1 H, NH-Ala), 4.97–4.89 (m, 1 H, 4-H), 4.24–4.12 (m, 1 H, CH-Ala), 3.76 (s, 3 H, Ph-OMe), 3.67–3.59 (m, 1 H, 5-H), 3.63 (s, 3 H, MeO-Ala), 3.15–3.07 (m, 1 H, 5′-H), 2.39–2.27 (m, 1 H, 6-H), 1.39 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 0.96 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.87 (d, $^3J_{H,H}$ = 6.7 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.99 ppm. (S_P)-**11f**: Product (S_P)-**11f** was obtained as a colorless oil (0.05 g, 5%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.20 (m, 1 H, Ar), 6.93–6.85 (m, 2 H, Ar), 6.79–6.74 (m, 1 H, Ar), 5.40 (dd, $^2J_{H,P}$ = 8.8 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH-Ala), 4.63–4.57 (m, 1 H, 4-H), 4.33–4.22 (m, 1 H, CH-Ala), 3.79 (s, 3 H, Ph-OMe), 3.72 (s, 3 H, MeO-Ala), 3.18 (dd, $^2J_{H,H}$ = 11.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, 5-H), 2.99–2.93 (m, 1 H, 5′-H), 2.39–2.27 (m, 1 H, 6-H), 1.39 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala), 0.99 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 0.96 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.31 ppm.

(R_P)-11h and (S_P)-11h: General Procedure B was applied by using compound **5h** (1.04 g, 2.80 mmol), L-alanine methyl ester hydrochloride (**9**, 0.39 g, 2.80 mmol), and NEt_3 (1.17 mL, 8.40 mmol) in CH_2Cl_2 (4.0 mL). (R_P)-**11h**: Product (R_P)-**11h** was obtained as a colorless oil (0.16 g, 13%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.53 (m, 1 H, Ar), 7.43–7.39 (m, 1 H, Ar), 7.26–7.21 (m, 1 H, Ar), 7.14–7.09 (m, 1 H, Ar), 5.36 (dd, $^2J_{H,P}$ = 8.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, NH-Ala), 5.07–5.01 (m, 1 H, 4-H), 4.26–4.18 (m, 1 H, CH-Ala), 3.68 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 5-H), 3.66 (s, 3 H, MeO-Ala), 3.23–3.17 (m, 1 H, 5′-H), 2.64–2.54 (m, 1 H, 6-H), 1.44 (d, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me-Ala), 1.12 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 1.05 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.38 ppm. (S_P)-**11h**: Product (S_P)-**11h** was obtained as a colorless oil (0.10 g, 8%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 2 H, Ar), 7.25–7.21 (m, 1 H, Ar), 7.16–7.10 (m, 1 H, Ar), 5.37 (dd, $^2J_{H,P}$ = 8.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, NH-Ala), 4.86–4.80 (m, 1 H, 4-H), 4.32–4.23 (m, 1 H, CH-Ala), 3.72 (s, 3 H, MeO-Ala), 3.59 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 5-H), 3.13–3.08 (m, 1 H, 5′-H), 2.46–2.36 (m, 1 H, 6-H), 1.39 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 1.05 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 1.01 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.77 ppm.

(R_P)-11i and (S_P)-11i: General Procedure B was applied by using compound **5i** (0.61 g, 1.65 mmol), L-alanine methyl ester hydrochloride (**9**, 0.23 g, 1.65 mmol), and NEt_3 (0.68 mL, 4.94 mmol) in CH_2Cl_2 (2.3 mL). (R_P)-**11i**: Product (R_P)-**11i** was obtained as a colorless oil (0.13 g, 18%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 1 H, Ar), 7.29–7.15 (m, 3 H, Ar), 5.12 (dd, $^2J_{H,P}$ = 8.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, NH-Ala), 4.98–4.91 (m, 1 H, 4-H), 4.24–4.11 (m, 1 H, CH-Ala), 3.70–3.62 (m, 1 H, 5-H), 3.66 (s, 3 H, MeO-Ala), 3.17–3.11 (m, 1 H, 5′-H), 2.40–2.28 (m, 1 H, 6-H), 1.42 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, Me-Ala), 0.99 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.91 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.64 ppm. (S_P)-**11i**: Product (S_P)-**11i** was obtained as a colorless oil (0.05 g, 7%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.31 (m, 1 H, Ar), 7.31–7.27 (m, 1 H, Ar), 7.22–7.17 (m, 2 H, Ar), 5.38 (dd, $^2J_{H,P}$ = 8.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, NH-Ala), 4.69–4.61 (m, 1 H, 4-H), 4.33–4.19 (m, 1 H, CH-Ala), 3.73 (s, 3 H, MeO-Ala), 3.29 (dd, $^2J_{H,H}$ = 11.7 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, 5-H), 3.05–2.98 (m, 1 H, 5′-H), 2.40–2.27 (m, 1 H, 6-H), 1.37 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 1.01 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, 7-H or 8-H), 0.98 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.34 ppm.

(R_P)-11j and (S_P)-11j: General Procedure B was applied by using compound **5j** (0.78 g, 2.12 mmol), L-alanine methyl ester hydrochloride (**9**, 0.30 g, 2.12 mmol), and NEt_3 (0.89 mL, 6.36 mmol) in CH_2Cl_2 (3.0 mL). (R_P)-**11j**: Product (R_P)-**11j** was obtained as a colorless oil (0.21 g, 23%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 4 H, Ar), 5.12 (dd, $^2J_{H,P}$ = 8.4 Hz, $^3J_{H,H}$ = 8.4 Hz, 1 H, NH-Ala), 4.92–4.85 (m, 1 H, 4-H), 4.16–4.07 (m, 1 H, CH-Ala), 3.63–3.57 (m, 1 H, 5-H), 3.60 (s, 3 H, MeO-Ala), 3.17–3.09 (m, 1 H, 5′-H), 2.33–2.20 (m, 1 H, 6-H), 1.42 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, Me-Ala), 0.99 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, 7-H or 8-H), 0.89 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.58 ppm. (S_P)-**11j**: Product (S_P)-**11j** was obtained as a colorless oil (0.11 g, 6%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 4 H, Ar), 5.39 (dd, $^2J_{H,P}$ = 8.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, NH-Ala), 4.67–4.56 (m, 1 H, 4-H), 4.32–4.18 (m, 1 H, CH-Ala), 3.73 (s, 3 H, MeO-Ala), 3.25 (dd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 3.04–2.94 (m, 1 H, 5′-H), 2.39–2.26 (m, 1 H, 6-H), 1.38 (d, $^3J_{H,H}$

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= 7.3 Hz, 3 H, Me-Ala), 0.99 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.97 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.43 ppm.

(R_P)-11k and (S_P)-11k: General Procedure B was applied by using compound **5k** (1.47 g, 3.56 mmol), L-alanine methyl ester hydrochloride (**9**, 0.50 g, 3.56 mmol), and NEt_3 (1.50 mL, 10.68 mmol) in CH_2Cl_2 (5.1 mL). (R_P)-**11k**: Product (R_P)-**11k** was obtained as a colorless oil (0.29 g, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.41 (m, 2 H, Ar), 7.21–7.17 (m, 2 H, Ar), 5.11 (dd, $^2J_{H,P}$ = 8.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH-Ala), 4.96–4.91 (m, 1 H, 4-H), 4.22–4.12 (m, 1 H, CH-Ala), 3.68–3.63 (m, 1 H, 5-H), 3.66 (s, 3 H, MeO-Ala), 3.15–3.12 (m, 1 H, 5′-H), 2.36–2.27 (m, 1 H, 6-H), 1.41 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, Me-Ala), 0.98 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H), 0.89 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.66 ppm. (S_P)-**11k**: Product (S_P)-**11k** was obtained as a colorless oil (0.07 g, 4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.43 (m, 2 H, Ar), 7.22–7.17 (m, 2 H, Ar), 5.39 (dd, $^2J_{H,P}$ = 8.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, NH-Ala), 4.63–4.58 (m, 1 H, 4-H), 4.32–4.20 (m, 1 H, CH-Ala), 3.73 (s, 3 H, MeO-Ala), 3.24 (dd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H), 3.01–2.98 (m, 1 H, 5′-H), 2.38–2.27 (m, 1 H, 6-H), 1.38 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, Me-Ala), 0.99 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 0.97 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.33 ppm.

(R_P)-11m and (S_P)-11m: General Procedure B was applied by using compound **5m** (0.77 g, 1.99 mmol), L-alanine methyl ester hydrochloride (**9**, 0.28 g, 1.99 mmol), and NEt_3 (0.83 mL, 5.97 mmol) in CH_2Cl_2 (2.8 mL). (R_P)-**11m**: Product (R_P)-**11m** was obtained as a colorless oil (0.28 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.75 (m, 4 H, Ar), 7.51–7.42 (m, 3 H, Ar), 5.17 (dd, $^2J_{H,P}$ = 8.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH-Ala), 5.02–4.96 (m, 1 H, 4-H), 4.26–4.15 (m, 1 H, CH-Ala), 3.67 (dd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 9.3 Hz, 1 H, 5-H), 3.52 (s, 3 H, MeO-Ala), 3.16–3.13 (m, 1 H, 5′-H), 2.44–2.34 (m, 1 H, 6-H), 1.43 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 0.98 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H), 0.85 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.60 ppm. (S_P)-**11m**: Product (S_P)-**11m** was obtained as a colorless solid (0.05 g, 6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.74 (m, 4 H, Ar), 7.53–7.44 (m, 3 H, Ar), 5.46 (dd, $^2J_{H,P}$ = 8.8 Hz, $^3J_{H,H}$ = 8.8 Hz, 1 H, NH-Ala), 4.65–4.60 (m, 1 H, 4-H), 4.37–4.25 (m, 1 H, CH-Ala), 3.73 (s, 3 H, MeO-Ala), 3.07 (dd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 2.93–2.90 (m, 1 H, 5′-H), 2.40–2.30 (m, 1 H, 6-H), 1.38 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala), 0.99 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H), 0.97 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.52 ppm.

(R_P)-12b and (S_P)-12b: General Procedure B was applied by using compound **5b** (0.52 g, 1.49 mmol), L-alanine benzyl ester hydrochloride (**10**, 0.32 g, 1.49 mmol), and NEt_3 (0.62 mL, 4.5 mmol) in CH_2Cl_2 (2.1 mL). (R_P)-**12b**: Product (R_P)-**12b** was obtained as a colorless oil (0.40 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 6 H, Ar), 7.19–7.02 (m, 3 H, Ar), 5.27 (dd, $^2J_{H,P}$ = 8.5 Hz, $^3J_{H,H}$ = 8.5 Hz, 1 H, NH-Ala), 5.14–4.99 (m, 3 H, 4-H, CH_2-Bn), 4.31–4.16 (m, 1 H, CH-Ala), 3.66 (dd, $^2J_{H,H}$ = 11.3 Hz, $^3J_{H,H}$ = 9.5 Hz, 1 H, 5-H), 3.21–3.14 (m, 1 H, 5′-H), 2.57–2.46 (m, 1 H, 6-H), 2.34 (s, 3 H, Ph-Me), 1.44 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, Me-Ala), 1.08 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H), 1.04 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.95 ppm. (S_P)-**12b**: Product (S_P)-**12b** was obtained as a colorless oil (0.12 g, 16%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5 H, Ar), 7.22–7.03 (m, 4 H, Ar), 5.45 (dd, $^2J_{H,P}$ = 8.6 Hz, $^3J_{H,H}$ = 8.6 Hz, 1 H, NH-Ala), 5.16 (s, 2 H, CH_2-Bn), 4.79–4.72 (m, 1 H, 4-H), 4.39–4.28 (m, 1 H, CH-Ala), 3.46 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 8.4 Hz, 1 H, 5-H), 3.06–3.00 (m, 1 H, 5′-H), 2.37–2.33 (m, 1 H, 6-H), 2.35 (s, 3 H, Ph-Me), 1.40 (d, $^3J_{H,H}$ = 7.3 Hz, 3 H, Me-Ala), 0.96 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.95 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 0.65 ppm.

(R_P)-12d and (S_P)-12d: General Procedure B was applied by using compound **5d** (0.72 g, 2.0 mmol), L-alanine benzyl ester hydrochloride (**10**, 0.44 g, 2.0 mmol), and NEt_3 (0.85 mL, 6.1 mmol) in CH_2Cl_2 (2.9 mL). (R_P)-**12d**: Product (R_P)-**12d** was obtained as a colorless oil (0.70 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 3 H, Ar), 7.31–7.27 (m, 2 H, Ar), 7.20–7.14 (m, 2 H, Ar), 7.11–7.04 (m, 2 H, Ar), 5.17–5.07 (m, 3 H, NH-Ala, CH_2-Bn), 4.98–4.89 (m, 1 H, 4-H), 4.31–4.15 (m, 1 H, CH-Ala), 3.63 (dd, $^2J_{H,H}$ = 11.6 Hz, $^3J_{H,H}$ = 9.6 Hz, 1 H, 5-H), 3.14–3.08 (m, 1 H, 5′-H), 2.39–2.32 (m, 1 H, 6-H), 2.30 (s, 3 H, Ph-Me), 1.44 (d, $^3J_{H,H}$ = 7.4 Hz, 3 H, Me-Ala), 0.98 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H), 0.88 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = –0.84 ppm. (S_P)-**12d**: Product (S_P)-**12d** was obtained as a colorless oil (0.055 g, 5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 5 H, Ar), 7.14–7.09 (m, 2 H, Ar), 7.08–7.02 (m, 2 H, Ar), 5.34 (dd, $^2J_{H,P}$ = 8.3 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, NH-Ala), 5.09 (s, 2 H, CH_2-Bn), 4.54–4.46 (m, 1 H, 4-H), 4.31–4.19 (m, 1 H, CH-Ala), 3.08 (dd, $^2J_{H,H}$ = 11.4 Hz, $^3J_{H,H}$ = 8.3 Hz, 1 H, 5-H), 2.89–2.83 (m, 1 H, 5′-H), 2.25 (s, 3 H, Ph-Me), 2.24–2.15 (m, 1 H, 6-H), 1.32 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala), 0.85 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, 7-H or 8-H), 0.83 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, 7-H or 8-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 1.44 ppm.

(S_P)-16j: General Procedure C was applied by using compound (R_P)-**11j** (0.21 g, 0.47 mmol), d4T (**15**, 0.16 g, 0.70 mmol), *tert*-butylmagnesium chloride (0.83 mL, 1.41 mmol), and THF/CH_3CN (6.2 mL). Product (S_P)-**16j** was obtained as a colorless foam (0.047 g, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br. s, 1 H, NH), 7.32–7.27 (m, 3 H, Ar), 7.15–7.09 (m, 2 H, Ar, 6-H), 7.04–6.99 (m, 1 H, 1′-H), 6.38–6.32 (m, 1 H, 2′-H), 5.93–5.87 (m, 1 H, 3′-H), 5.08–5.00 (m, 1 H, 4′-H), 4.41–4.27 (m, 2 H, 5′-H), 4.01–3.88 (m, 1 H, CH-Ala), 3.71 (s, 3 H, MeO-Ala), 3.59 (dd, $^2J_{H,P}$ = 10.5 Hz, $^3J_{H,H}$ = 10.5 Hz, 1 H, NH-Ala), 1.82 (s, 3 H, Me-Th), 1.32 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.13, 2.59 (*dr* = 37:1; 95% *de*) ppm.

(R_P)-16j: General Procedure C was applied by using compound (S_P)-**11j** (0.05 g, 0.10 mmol), d4T (**15**, 0.04 g, 0.16 mmol), *tert*-butylmagnesium chloride (0.18 mL, 0.31 mmol), and THF/CH_3CN (1.4 mL). Product (R_P)-**16j** was obtained as a colorless foam (0.014 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (br. s, 1 H, NH), 7.32–7.27 (m, 2 H, Ar), 7.23–7.19 (m, 1 H, 6-H), 7.18–7.12 (m, 2 H, Ar), 7.04–6.98 (m, 1 H, 1′-H), 6.32–6.26 (m, 1 H, 2′-H), 5.96–5.87 (m, 1 H, 3′-H), 5.06–4.95 (m, 1 H, 4′-H), 4.34–4.20 (m, 2 H, 5′-H), 4.03–3.91 (m, 1 H, CH-Ala), 3.75–3.67 (m, 1 H, NH-Ala), 3.71 (s, 3 H, MeO-Ala), 1.87 (d, $^4J_{H,H}$ = 1.4 Hz, 3 H, Me-Th), 1.36 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 2.62 ppm.

(S_P)-16k: General Procedure C was applied by using compound (R_P)-**11k** (0.15 g, 0.32 mmol), d4T (**15**, 0.11 g, 0.48 mmol), *tert*-butylmagnesium chloride (0.56 mL, 0.96 mmol), and THF/CH_3CN (4.3 mL). Product (S_P)-**16k** was obtained as a colorless foam (0.026 g, 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (br. s, 1 H, NH), 7.43 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, Ar), 7.29–7-27 (m, 1 H, 6-H), 7.07 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, Ar), 6.37–6.32 (m, 1 H, 2′-H), 5.92–5.86 (m, 1 H, 3′-H), 5.07–5.00 (m, 1 H, 4′-H), 4.40–4.27 (m, 2 H, 5′-H), 4.03–3.90 (m, 1 H, CH-Ala), 3.77–3.64 (m, 1 H, NH-Ala), 3.71 (s, 3 H, MeO-Ala), 1.82 (s, 3 H, Me-Th), 1.32 (d, $^3J_{H,H}$ =

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7.1 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.13, 2.54 (*dr* = 27:1; 93% *de*) ppm.

(R_P)-16k: General Procedure C was applied by using compound (S_P)-**11k** (0.13 g, 0.26 mmol), d4T (**15**, 0.09 g, 0.39 mmol), *tert*-butylmagnesium chloride (0.46 mL, 0.79 mmol), and THF/CH_3CN (3.5 mL). Product (R_P)-**16k** was obtained as a colorless foam (0.074 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (br. s, 1 H, NH), 7.46–7.40 (m, 2 H, Ar), 7.21 (d, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H), 7.12–7.06 (m, 2 H, Ar), 7.02–6.98 (m, 1 H, 1′-H), 6.32–6.24 (m, 1 H, 2′-H), 5.94–5.87 (m, 1 H, 3′-H), 5.03–4.96 (m, 1 H, 4′-H), 4.33–4.19 (m, 2 H, 5′-H), 4.03–3.91 (m, 1 H, CH-Ala), 3.80 (dd, $^2J_{H,P}$ = 11.3 Hz, $^3J_{H,H}$ = 9.5 Hz, 1 H, NH-Ala), 3.71 (s, 3 H, MeO-Ala), 1.86 (s, $^4J_{H,H}$ = 1.0 Hz, 3 H, Me-Th), 1.36 (d, $^3J_{H,H}$ = 7.0 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 2.58 ppm.

(S_P)-17b: General Procedure C was applied by using compound (R_P)-**12b** (0.22 g, 0.44 mmol), d4T (**15**, 0.15 g, 0.66 mmol), *tert*-butylmagnesium chloride (0.78 mL, 1.32 mmol), and THF/CH_3CN (5.9 mL). Product (S_P)-**17b** was obtained as a colorless foam (0.027 g, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (br. s, 1 H, NH), 7.39–7.28 (m, 6 H, Ar, 6-H), 7.24–6.98 (m, 5 H, Ar, 1′-H), 6.37–6.28 (m, 1 H, 2′-H), 5.93–5.83 (m, 1 H, 3′-H), 5.17 (d, $^2J_{H,H}$ = 12.1 Hz, 1 H, CH_2-Bn), 5.12 (d, $^2J_{H,H}$ = 12.1 Hz, 1 H, CH_2-Bn), 5.03–4.94 (m, 1 H, 4′-H), 4.39–4.18 (m, 2 H, 5′-H), 4.13–3.99 (m, 1 H, CH-Ala), 3.58 (dd, $^2J_{H,P}$ = 10.1 Hz, $^3J_{H,H}$ = 10.1 Hz, 1 H, NH-Ala), 2.24 (s, 3 H, Me-Ph), 1.75 (s, 3 H, Me-Th), 1.35 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 2.95 ppm.

(R_P)-17b: General Procedure C was applied by using compound (S_P)-**12b** (0.07 g, 0.14 mmol), d4T (**15**, 0.05 g, 0.22 mmol), *tert*-butylmagnesium chloride (0.26 mL, 0.45 mmol), and THF/CH_3CN (1.9 mL). Product (R_P)-**17b** was obtained as a colorless foam (0.018 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1 H, NH), 7.39–7.27 (m, 6 H, Ar), 7.22–7.19 (m, 1 H, 6-H), 7.18–7.02 (m, 4 H, Ar), 6.99–6.95 (m, 1 H, 1′-H), 6.23–6.17 (m, 1 H, 2′-H), 5.88–5.81 (m, 1 H, 3′-H), 5.10 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2-Bn), 5.05 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2-Bn), 4.94–4.88 (m, 1 H, 4′-H), 4.24–4.18 (m, 2 H, 5′-H), 4.10–3.98 (m, 1 H, CH-Ala), 3.72 (dd, $^2J_{H,P}$ = 10.4 Hz, $^3J_{H,H}$ = 10.4 Hz, 1 H, NH-Ala), 2.26 (s, 3 H, Me-Ph), 1.83 (s, 3 H, Me-Th), 1.39 (d, $^3J_{H,H}$ = 6.9 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 2.62 ppm.

(S_P)-17d: General Procedure C was applied by using compound (R_P)-**12d** (0.16 g, 0.33 mmol), d4T (**15**, 0.11 g, 0.49 mmol), *tert*-butylmagnesium chloride (0.57 mL, 0.98 mmol), and THF/CH_3CN (4.4 mL). Product (S_P)-**17d** was obtained as a colorless foam (0.025 g, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (br. s, 1 H, NH), 7.38–7.28 (m, 6 H, Ar, 6-H), 7.10–6.98 (m, 5 H, Ar, 1′-H), 6.33–6.29 (m, 1 H, 2′-H), 5.87–5.82 (m, 1 H, 3′-H), 5.14 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2-Bn), 5.10 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2-Bn), 4.99–4.94 (m, 1 H, 4′-H), 4.36–4.21 (m, 2 H, 5′-H), 4.08–3.96 (m, 1 H, CH-Ala), 3.60 (dd, $^2J_{H,P}$ = 10.8 Hz, $^3J_{H,H}$ = 10.8 Hz, 1 H, NH-Ala), 2.29 (s, 3 H, Me-Ph), 1.79 (s, 3 H, Me-Th), 1.32 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 3.18, 2.26 (*dr* = 33:1; 94% *de*) ppm.

(R_P)-17d: General Procedure C was applied by using compound (S_P)-**12d** (0.11 g, 0.24 mmol), d4T (**15**, 0.08 g, 0.35 mmol), *tert*-butylmagnesium chloride (0.41 mL, 0.70 mmol), and THF/CH_3CN (3.1 mL). Product (R_P)-**17d** was obtained as a colorless foam (0.058 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (br. s, 1 H, NH), 7.40–7.29 (m, 5 H, Ar), 7.25–7.22 (m, 1 H, 6-H), 7.12–7.02 (m, 4 H, Ar), 7.00–6.95 (m, 1 H, 1′-H), 6.22–6.17 (m, 1 H, 2′-H), 5.88–5.82 (m, 1 H, 3′-H), 5.15 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2-Bn), 5.13 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, CH_2-Bn), 4.97–4.90 (m, 1 H, 4′-H), 4.29–4.15 (m, 2 H, 5′-H), 4.07–3.95 (m, 1 H, CH-Ala), 3.56 (dd, $^2J_{H,P}$ = 11.1 Hz, $^3J_{H,H}$ = 9.7 Hz, 1 H, NH-Ala), 2.30 (s, 3 H, Me-Ph), 1.84 (s, $^4J_{H,H}$ = 1.0 Hz, 3 H, Me-Th), 1.36 (d, $^3J_{H,H}$ = 7.1 Hz, 3 H, Me-Ala) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 2.62 ppm.

Antiretroviral Evaluation: Human immunodeficiency virus type 1 (HIV-1) was originally obtained from a persistently HIV-infected H9 cell line, as described previously, and was kindly provided by Dr. R. C. Gallo (then at the National Institutes of Health, Bethesda, MD). Virus stocks were prepared from the supernatants of HIV-1-infected MT-4 cells. HIV-2 (strain ROD) was kindly provided by Dr. L. Montagnier (then at the Pasteur Institute, Paris, France), and virus stocks were prepared from the supernatants of HIV-2-infected MT-4 cells. CEM cells were obtained from the American Tissue Culture Collection (Rockville, MD). CEM cells were infected with HIV as described previously.[18] Briefly, 4×10^5 CEM cells/mL were infected with HIV-1(III_B) or HIV-2(ROD) at approximately 100 $CCID_{50}$ (50% cell culture infective dose) per mL of cell suspension. The thymidine kinase deficient CEM cell cultures were also infected with HIV-2(ROD). Then, the infected cell suspensions (100 μL) were transferred into 96-well microtiter plate wells and mixed with the appropriate dilutions of the test compounds (100 μL). After 4–5 d, giant cell formation was recorded microscopically in the HIV-infected cell cultures. The 50% effective concentration was defined as the compound concentration required to inhibit virus-induced cytopathicity by 50%. The 50% cytostatic concentration was defined as the compound concentration required to block CEM cell proliferation by 50%, as derived by counting the cell numbers from CEM cell cultures exposed to different compound concentrations by using a Coulter Particle Counter ZI (Analysis, Gent, Belgium).

Supporting Information (see footnote on the first page of this article): ^{13}C NMR spectroscopic data; mass spectrometric data; analytical HPLC data of phosphoramidate prodrugs **16j**,**k** and **17b**,**d**.

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